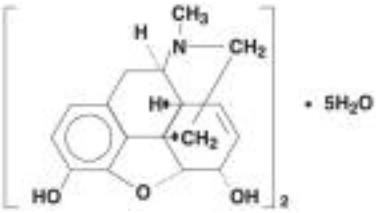
MORPHINE SULFATE - morphine sulfate injection
Meridian Medical Technologies™, Inc.

CII
(Warning: May be habit forming)
Rx Only
A sterile solution of morphine for intramuscular injection contained in a unit-dose auto-injector system.

DESCRIPTION
Morphine is one of the naturally occurring phenanthrene alkaloids of opium derived from the opium poppy; it is classified pharmacologically as a narcotic analgesic. Morphine sulfate may be designated chemically as 7,8-didehydro-4,5a- epoxy- 17 methyl-morphinan-3,6adiol sulfate (2:1) (salt) pentahydrate, with the following structural formula:



Morphine sulfate occurs as white, feathery, silky crystals, cubical masses of crystals, or white crystalline powder; it is soluble in water and slightly soluble in alcohol. Morphine has a pKa of 7.9 with an octanol/water partition coefficient of 1.42 at pH 7.4. At this pH, the tertiary amino group is mostly ionized, making the molecule water soluble. Morphine is significantly more water soluble than any other opiod in clinical use.
The auto-injection dispenses 10 mg morphine sulfate in 0.7 mL Water for Injection USP, with 10.5 mg benzyl alcohol and 0.7 mg edetate disodium. Sulfuric acid may be added to adjust pH. The pH range is 2.5 - 6.0.

CLINICAL PHARMACOLOGY
Morphine is the prototype of many narcotic drugs that interact predominantly with the opiod μ-receptor. These μ-binding sites are very discretely distributed in the human brain, with high densities in the posterior amygdala, hypothalmamus, thalamus, mucleus caudatus, putamen, and certain cortical areas. They are also found on the terminal axons at primary afferents within laminae I and II (substantia gelatinosa) of the spinal cord and in the spinal nucleus at the trigeminal nerve. Morphine may produce analgesia by acting at any, all, or some combination of the periaqueductal-periventricular gray matter, the ventromedial medulla, and the spinal cord.
In clinical settings, morphine exerts its principal pharmacological effects on the central nervous system and gastrointestinal tract. Its primary actions of therapeutic value are analgesia and sedation. Morphine appears to increase the patient's tolerance for pain and to decrease the perception of suffering, although the presence of the pain itself may still be recognized.
In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Morphine depresses various respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood levels of morphine may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients as is postural syncope.
Morphine increases the tone and decreases the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time is responsible for the constipating effect of morphine. Because morphine may increase biliary-tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.
While morphine generally increases the tone of urinary-tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.
In therapeutic dosage, morphine does not usually exert major effects on the cardiovascular system. However, some patients exhibit a propensity to develop orthostatic hypotension and fainting. Rapid intravenous injection is more likely to precipitate a fall in blood pressure than are intramuscular or subcutaneous injections.
Morphine can cause histamine release, which appears to be responsible for wheals or urticaria sometimes seen at the site of injection. Histamine release may also produce dilation of cutaneous blood vessels, with resultant flushing of the face and neck, pruritus and sweating.

Pharmacokinetics
Morphine is completely absorbed following intramuscular administration and has an apparent volume of distribution ranging from 1.0 to 4.7 L/kg. Peak plasma levels for a 70 kg adult following intramuscular administration of 10 mg of morphine are between 30-140 ng/mL. (The minimum effective analgesic concentration of morphine is 20-40 ng/mL in studies of patient-controlled analgesia.) A blood-brain barrier exists for the drug with plasma concentrations of morphine remaining higher than the corresponding CSF morphine levels following intramuscular administration. Morphine circulates unbound in plasma, with a mean total plasma clearance which ranges from 0.9 to 1.2 L/kg/hr in post-operative patients. The major pathway of clearance is hepatic glucuronidation to morphine-3-glucuronide, which is pharmacologically inactive. The major excretion path of the conjugate is through the kidneys, with about 10%

in the feces. Morphine is also eliminated by the kidneys, 2 to 12% being excreted unchanged in the urine. The terminal half-life in normal patients is 1.5 to 2.0 hours.

Pharmacodynamics
Onset of analgesia occurs within 5-20 minutes following intramuscular administration of morphine, rising to peak analgesia sixty minutes after a single intramuscular injection. The duration of analgesia after a single injection is usually three to four hours. Morphine and similar opioid analgesics rapidly induce tolerance to their effects, so that the duration of analgesia may be shorter following subsequent doses of morphine. Once patients are started on morphine, the dose required for satisfactory analgesia will rise, with the rate of development of tolerance varying depending on the patient's prior narcotic use, level of pain, degree of anxiety, use of other CNS active drugs, circulatory status, total dose, and the inter-dose interval.

INDICATIONS AND USAGE
Morphine Sulfate Injection, USP (Auto-Injector) provides morphine sulfate in a sterile solution for intramuscular injection for the management of pain.

CONTRAINDICATIONS
This product is contraindicated in patients with a known hypersensitivity to morphine.

WARNINGS
THE MORPHINE AUTO-INJECTOR SYSTEM WAS DEVELOPED FOR USE UNDER CONDITIONS WHICH REQUIRE AN AUTOMATIC INJECTION DEVICE. IT CARRIES A LOW RISK OF INADVERTENT INTRAVASCULAR INJECTION AND INJECTION SITE REACTIONS. IT IS PREFERABLE TO DELIVER MORPHINE BY STANDARD HOSPITAL TECHNIQUES WHEN CONDITIONS PERMIT.

PRECAUTIONS

Head Injury and Increased Intracranial Pressure
Morphine should be used with caution in patients with increased intracranial pressure or with head injury. Pupillary changes (miosis) from morphine as well as adverse effects (vomiting, bradycardia) may obscure the existence, extent, and course of intracranial pathology.

Pulmonary Disorders
Care is urged in using this drug in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis, or paralysis of the phrenic nerve). Morphine should be used with caution in patients with asthma, chest wounds, upper airway obstruction, or in any other acute or chronic pulmonary disorder because of the known risk of acute respiratory failure following morphine administration in such patients.

Hypotensive Effect
The administration of morphine may result in severe hypotension in an individual whose ability to maintain their blood pressure has been compromised by blood loss or shock. In addition, morphine may produce orthostatic hypotension (syncope) in ambulatory patients and make it difficult for such cases to ambulate if necessary for medical evacuation.

Use in Billary Disorders
Therapeutic administration of morphine may result in smooth muscle hypertonicity which can aggravate or induce biliary colic.

Exposure, Hypothermia, Immersion, and Shock
Caution must be used when injecting any opioid intramuscularly into chilled areas or in patients with hypotension or shock, since impaired perfusion may prevent complete absorption; if repeated injections are administered, an excessive amount may be suddenly absorbed if normal circulation is re-established.

Use With Other CNS Depressants or Alcohol:
The depressant effects of morphine are potentiated by the presence of other CNS depressants such as alcohol, sedatives, antihistaminics, or psychotropic drugs. Use of morphine in conjunction with other CNS active drugs may increase the risk of respiratory depression.

Information For Patients
Analgesic doses of morphine cloud judgement and impair the mental and/or physical abilities which are required for the performance of tasks such as driving a vehicle or operating machinery. The concomitant use of alcohol or other central nervous systems depressants, including sedatives, hypnotics, tranquilizers, phenothiazines and antihistamines, may have an additive effect. Morphine, like other narcotic analgesics, may produce orthostatic hypotension in ambulatory patients. Patients should be cautioned accordingly.

Drug Interactions
Morphine should be administered cautiously to avoid additive effects when other central nervous system depressants, including other narcotic analgesics, general anesthetics, phenothiazines, tricyclic antidepressants, tranquilizers, and alcohol are given concomitantly.

Drug/Laboratory Test Interactions
Because narcotic analgesics may increase biliary-tract pressure, with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after a narcotic analgesic has been given. In addition, an intramuscular injection may cause a mild increase in SGOT and CPK due to muscle injury at the site of injection. Morphine, like other opiods, will give a positive test for narcotics in the urine of any patient who has received it for a few days to a week, depending on the sensitivity of the assay procedure.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Morphine is without known carcinogenic or mutagenic effects, and is not known to impair fertility in animals, however, morphine has not been tested for these effects by methods meeting modern standards.

Teratogenic Effects, Pregnancy Category C
Morphine sulfate is not teratogenic in rats at 35 mg/kg/day (thirty-five times the usual human dose), but does result in increased pup mortality and growth retardation at doses that narcotize the mother (> 10mg/kg/day, ten times the usual human dose).

Use in Pregnancy
This product should only be given to pregnant women when no safer method of controlling severe pain is available and the potential risks are acceptable when considered in terms of the clinical benefit. If this product is used in late pregnancy, personnel, equipment and drugs (including pediatric naloxone) to resuscitate the newborn should be at hand.

Labor And Delivery
This product is intended for fixed-dose administration by non-medical personnel and is not recommended for routine obstetrical analgesia.

Nursing Mothers
Morphine crosses into breast milk in variable concentration and use of this product in nursing mothers should be guided by the relative risk of narcotic effects in the infant and the maternal need for analgesia.

Pediatric Use
The morphine Auto-Injector delivers a fixed dose of 10 mg at a fixed injection depth and volume. In consequences, it was not designed for use in pediatric patients under the age of 14 or weighing less than 40 kilos (90 lb).

Use In The Aged
The pharmacodynamic effects of morphine in the aged are more variable than in the younger population. Older patients will vary widely in the effective initial dose, rate of development of tolerance, and the frequency and magnitude of associated adverse effects. Use of this product in the aged should be accompanied by an appreciation of the increased risks involved with its use in this population.

ADVERSE REACTIONS
The major hazards of morphine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest have occurred, particularly with overdosage, rapid intravenous administration, and pre-existing hypovolemic shock. Rarely, anaphylactoid reactions have been reported when morphine or other phenanthrene alkaloids of opium are administered intravenously.
The most frequently observed adverse reactions include sedation, lightheadedness, dizziness, nausea. vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down. (see also PRECAUTIONS "Hypotensive Effect").
Other possible adverse reactions include:
Central Nervous System - Euphoria, dysphoria, weakness, headache. agitation, tremor, uncoordinated muscle movements, visual disturbances. transient hallucinations and disorientation.
Gastrointestinal - Constipation, biliary tract spasm.
Cardiovascular - Tachycardia, bradycardia, palpitation, faintness, syncope, and orthostatic hypotension.
Genitourinary - Oliguria and urinary retention; an antidiuretic effect has been reported.
Allergic - Allergic reactions to opiates occur infrequently; pruritus, urticaria. and other skin rashes are most common. Rarely, anaphylactoid reactions have been reported following intravenous administration.
Other - Opiate-induced histamine release may be responsible for the flushing of the face, sweating, and pruritus often seen with these drugs. Wheals and urticaria at the site of injection are probably related to histamine release. Local tissue irritation, pain and induration

have been reported following repeated subcutaneous injection. Morphine, like other opioids, may alter temperature regulation in susceptible individuals and will depress the cough reflex.

DRUG ABUSE AND DEPENDENCE

Controlled Substance CII

Morphine sulfate is a Schedule **II** narcotic under the United States Controlled Substance Act (21 U.S.C. 801-886). Morphine is the most commonly cited prototype for narcotic substances that possess an addiction-forming or addiction-sustaining liability. As with all potent opioids which are μ-agonists, tolerance, psychological and physical dependence to morphine may develop. Individuals with a prior history of opioid or other substance abuse or dependence would be considered to be at greater risk. Care must be taken to avert withdrawal in patients who have been maintained on parenteral/oral narcotics. Withdrawal symptoms may occur when morphine is discontinued abruptly or upon administration of a narcotic antagonist.

Withdrawal symptoms in patients dependent on morphine begin shortly before the time of the next scheduled dose, reach a peak at 36 to 72 hours after the last dose, and then slowly subside over a period of 7 to 10 days. Symptoms include yawning, sweating, lacrimation. rhinorrhea, a restless, tossing sleep, dilated pupils, gooseflesh, irritability, tremor, nausea, vomiting, and diarrhea. Treatment of the abstinence syndrome is primarily symptomatic and supportive, including maintenance of proper fluid and electrolyte balance.

OVERDOSAGE

Overdosage of morphine is characterized by respiratory depression, with or without concomitant CNS depression. Mild overdosage may be managed by continuous stimulation of the patient and/or frequent verbal instructions to "Wake-up" or "Take a deep breath". Serious overdose with morphine is characterized by profound respiratory depression (a decrease in respiratory rate/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils and respiratory depression is strongly suggestive of opiate poisoning.

Primary attention should be given to the establishment of adequate respiratory exchange through maintenance of a patent airway and institution of assisted, or controlled, ventilation. The narcotic antagonist, naloxone, is a specific antidote. An initial dose of 0.4 to 2 mg of naloxone should be administered intravenously, simultaneously with respiratory resuscitation. If the desired degree of counteraction and improvement in respiratory function is not obtained, naloxone may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of morphine-induced toxicity should be questioned. Intramuscular or subcutaneous administration of naloxone may be used if the intravenous route is not available. As the duration of effect of naloxone is considerably shorter than that of morphine, repeated administration may be necessary.

DOSAGE AND ADMINISTRATION

The morphine Auto-Injector delivers a fixed dose of 10 mg which will generally provide adequate analgesia for a 70 kg adult. Onset of analgesia is usually within 5-20 minutes and peak analgesia will be reached in one hour. Although a single injection will usually provide appropriate relief for most individuals of normal stature, individuals who do not obtain adequate pain relief after 30 minutes may require a second dose.

The Auto-Injector is not intended for repeated administration, but if repeated doses must be given using the device, the usual adult dosage for repeated administration is one injector (10 mg) every 4 hours as needed to control the pain.

DIRECTIONS FOR USING THE AUTO-INJECTOR

1. Remove red safety.

2. Place purple end on patient's outer thigh and push the unit firmly against the patient until injector functions.

HOW SUPPLIED

Morphine Sulfate Injection, USP Auto-Injector 10 mg/0.7 mL is available singly or in packages of five. For military use, the auto-injectors are supplied through the Directorate of Medical Materiel, Defense Supply Center Philadelphia or other analogous agency. When activated, each auto-injector dispenses 10 mg of morphine sulfate in 0.7 mL of a sterile solution containing 10.5 mg benzyl alcohol and 0.7 mg edetate disodium in Water for Injection. The pH is adjusted with sulfuric acid. The pH range is 2.5 - 6.0. The product is pyrogen free.

SAFETY AND HANDLING INSTRUCTIONS

The morphine Auto-Injector contains a spring-driven injection mechanism and is capable of inflicting injury if accidentally misused. The product should remain in its original container with the safety in place until actually in use, and in no case should the product be carried with the safety removed. Intramuscular or subcutaneous naloxone in the dosage of 0.4 mg is antidotal in case of accidental injection, but may have to be repeated at 30-60 minute intervals for several doses.

Caution Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

STORAGE

Store at 25°C (77°F); Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature] Avoid freezing.

Morphine Auto-Injectors have a significant risk of illicit diversion and should be handled strictly in accordance with current directives in order to assure their availability under emergency conditions.

Meridian Medical Technologies, Inc.
Columbia, MD 21046
0001000
10/03

10 mg AUTO-INJECTOR LABEL

MERIDIAN MEDICAL TECHNOLOGIES TM
Columbia, MO 21046, U.S.A.

A subsidiary of King Pharmaceuticals ® **, Inc.**
0001280
Rx Only
Store at 25°C(77°F); Excursions permitted to 15-30°C(59-86°F).
[See USP Controlled Room Temperature]. Avoid freezing.
MORPHINE SULFATE INJECTION, 10 mg
CII
1 REMOVE RED SAFETY CAP PLACE PURPLE END ON OUTER THIGH AND PUSH FIRMLY
2 MORPHINE AUTO-INJECTOR
NSN 6505-01-302-5530
3 NDC 11704 23501 9